IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	10/757,827
Applicants	:	M. ROSEN et al.
Filed	:	January 15, 2004
Title	:	Mesenchymal Stem Cells as a Vehicle for Ion Channel Transfer in Syncytial Structures
Confirmation No.	:	5518
Art Unit	:	1632
Examiner	:	Anoop Kumar SINGH
Docket No.	:	13533/48003
Customer No.	:	26646

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

S I R:

I, Dr. Michael R. Rosen, do hereby declare:

1. I am a professor of Pharmacology and of Pediatrics at the College of Physicians and Surgeons, Columbia University. For over thirty-five years, I have devoted my research efforts to basic cardiovascular research. My curriculum vitae is attached as Exhibit A.

2. I am co-inventor of the subject matter disclosed and currently claimed in the above-identified patent application ("the '827 application"). The invention disclosed in the '827 application relates to methods and compositions for expressing a hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel in a mammalian heart by engineering a mesenchymal stem cell (MSC) to express such a channel from an exogenous nucleic acid, and then delivering said MSCs to the mammalian heart. The HCN's properties enable it to spontaneously generate a

pacemaker current in the MSC delivered to the heart. Such a method has a variety of uses, including treatment of cardiac disorders that involve aberrant pacemaker function.

3. I understand that claims 49, 51, 56-57, 59, and 65-67 have been rejected by the Examiner. The claims recite methods of expressing a functional HCN2 ion channel in a mammalian heart, treating conduction block, complete or incomplete atrioventricular block, or sinus node dysfunction in a mammal, and inducing a pacemaker current in a mammal's heart or in a cardiomyocyte, by introducing directly into the mammal a composition comprising an MSC incorporated with a nucleic acid that encodes an HCN2 ion channel, wherein the MSC forms a gap junction with a cell of the heart. The Examiner maintains that one of skill in the art would not have been able to make and use the claimed invention in view of the specification.

4. The Examiner concedes that the specification provides guidance with respect to directly injecting hMSCs transfected with nucleic acid encoding HCN2 polypeptide into the anterior left ventricular wall of canine heart, resulting in expression of HCN2 and generation of pacemaker rhythm in the canine heart, and that the specification and the Plotnikov reference that the Applicants cited in the previous amendment (August 13, 2007) provide "adequate guidance for a method of inducing pacemaker current in mammalian heart."

5. Nevertheless, the Examiner finds several shortcomings in the application disclosure, including allegedly no connection between the disclosed injection of the MSC composition and delivery by any means such as topical, microinjection, catheter, allegedly no correlation of delivery to anterior left ventricular wall with delivery to any other part of the heart, such as the atrium or Purkinje system, and no evidence to support extrapolation of the canine model that the specification discloses to "any mammalian heart for therapeutic purpose without undue experimentation." According to the Examiner, "vagal stimulation in dogs does not represent a cardiac rhythm disorder in a mammal." *See* Office Action at 4-7.

6. The person of skill in the art to which the '827 application is directed would have had a Ph.D. or similar experience in molecular biology as it relates to cardiology or a related field, or an M.D. or similar experience with a specialty in cardiology or a related field, and an

understanding of the electrical conduction system of the heart and/or the functioning of ion channels and related proteins.

7. I have reviewed the disclosure of the '827 application and of Strauer et al., Circulation 106: 1913 (2002) (Exhibit B).

8. For reasons detailed below, based on my review of the application, as well as taking into consideration what was known in the art at the time the '827 application was originally filed (January 15, 2003), I conclude that the '827 application would have provided one of skill in the art sufficient guidance to practice the claimed methods without undue experimentation. The person of ordinary skill in the art, without undue experimentation, could have performed the methods disclosed by the application that entail the use of stems cells incorporated with HCN2 (as set forth below) using known alternative methods of cell delivery, including delivery topically, by microinjection, and by catheter, could have delivered cells to the heart by contacting a cell of the heart generally, and could have extrapolated to humans the disclosed methods that were performed successfully on a dog heart. Further, the person of ordinary skill in the art could have used the disclosed results in the canine model to determine the relative level of pacemaker function achieved by these various methods without undue experimentation.

9. The working examples of the specification demonstrate the successful administration of hMSCs incorporated with HCN2 to a canine heart via needle injection. *See* Application at ¶ 0030. The specification further discloses that other means of contacting the heart with such stem cells include topical application to heart cells, microinjection, and catheterization. *See id.* at ¶ 0086. These alternative means of administration were known to the person of ordinary skill in the art at the time of filing, and therefore could have been used by the person of ordinary skill in the art to administer the hMSCs to the heart. *See, e.g.*, Strauer et al., Circulation 106: 1913 (2002) (intracoronary catheter). Moreover, in view of the disclosed example, the person of ordinary skill in the art would have been able to determine without undue experimentation the level of pacemaker function obtained by such administration. Thus, following the teachings of the specification, and given the state of the art at the time the '827 application was filed, one

skilled in the art would have been able to administer MSCs incorporated with HCN2 to the heart using methods disclosed in the application without undue experimentation.

10. The working examples of the specification demonstrate induction of pacemaker current by hMSCs incorporated with HCN2 that were injected into the anterior left ventricular wall of a dog's heart. *See* Application at ¶ 0030. The specification further discloses that contacting a cell of the heart generally with such stem cells can treat a cardiac condition in a subject, such as conduction block, complete or incomplete atrioventricular block, and sinus node dysfunction, and can induce a current in the heart or a cell of a subject. *See id.* at ¶¶ 0081, 0083-0084, 0087, 0089. In view of the specification and given the relative skill of those in the art, the person of ordinary skill in the art would have been able to contact a cell of the heart with hMSCs incorporated with HCN2 and thereby treat such a condition or induce such a current. Moreover, in view of the disclosed example, the person of ordinary skill in the art would have been able to determine without undue experimentation the level of pacemaker function obtained following such contacting. Thus, following the teachings of the specification, and given the state of the art at the time the '827 application was filed, one skilled in the art would have been able to administer MSCs incorporated with HCN2 to a cell of the heart generally using methods disclosed in the application without undue experimentation.

11. The present application teaches how to generate a stable rhythm *in vivo* in a treated heart. For example, the application teaches the generation of stable rhythm in the heart of a dog in which sinus rhythm has been stopped by vagal stimulation (a recognized model of human bradycardia and other conditions characterized by aberrant heartbeat, *see below*). The generation of such a stable rhythm entailed introducing into the heart of the dog stem cells engineered to over-express HCN2. *See* Appln. at ¶ 0030 and Figure 10A-E, and at ¶¶ 0166-0173. At the time of filing, the person of ordinary skill in the art, guided by the Application, would have been able to induce a pacemaker current in a human heart without undue experimentation. At the time of filing, the person of ordinary skill in the art recognized the dog heart as a model for the human heart because of various similarities between them in important characteristics. For example, the dog heart and human heart have a similar range of heart rates (from about 40 to about 180 beats

per minute). They also exhibit similar autonomic responsiveness. In view of these and other important similarities, the dog heart has long been recognized as a model for the study of human heart diseases.

12. In summary, following the teachings of the specification, in light of the state of the art at the time the '827 application was filed coupled with the relative skill of those in the are, one skilled in the art would have been able to generate MSCs engineered to express the HCN2 channel and deliver said cells to the heart of a subject. Furthermore, although the levels of pacemaker current may vary based on the method of delivery or the region of the human heart to which the cells are delivered, undue experimentation would not be required to test for such pacemaker activity.

13. I, Dr. Michael Rosen, declare under penalty of perjury that the above statements are true and correct to the best of my knowledge, information, and belief. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: May 1, 2008

Michael R. Rosen, M.D.